REMARKS

Applicant thanks Examiner Chakrabarti for his helpful comments conveyed to Applicant's attorney, Janet M. MacLeod, in a telephone interview on December 22, 2003. Claims 1-8 and 10 were discussed, as was the reference U.S. Patent No. 5,547,843 to Studier et al. ("Studier et al."). No exhibits were shown and no demonstrations were conducted during the interview. Agreement was not reached.

In the Office Action mailed August 26, 2003, Claims 1-5 and 10 have been rejected under 35 U.S.C. § 103(a) as allegedly rendered obvious by Studier et al. Claims 6 and 7 have been rejected under 35 U.S.C. § 103(a) as allegedly rendered obvious by Studier et al in view of Nyren et al. (1985) Analytical Biochemistry 151:504-509 ("Nyren et al."). Claim 8 has been rejected under 35 U.S.C. § 103(a) as allegedly rendered obvious by Studier et al. in view of U.S. Patent No. 6,335,162 to Shultz et al. ("Shultz et al."). The Examiner has alleged that Studier et al. teach a method having the elements of Claim 1, but in which the nucleic acid binding protein is added before the hybridization of the primer to the sample nucleic acid, whereas in the claimed invention the order is reversed. It would have been obvious, the Examiner has alleged, to switch the order of mixing the ingredients.

Nyren et al. allegedly teach a method wherein the incorporation of the nucleotide is detected by monitoring the release of inorganic pyrophosphate. It would have been obvious, the Examiner has alleged, to use the detection method of Nyren et al. in the method of Studier et al. in order to improve the assay system.

Shultz et al. allegedly teach a method wherein apyrase is presented during a polymerization reaction. It would have been obvious, the Examiner has alleged, to combine the method of Shultz et al. with the method of Studier et al. in order to minimize background.

Applicants respectfully submit that it would not have been obvious to switch the order of mixing the ingredients in the method of Studier et al. Studier et al. disclose a method for promoting "specific alignment of primers on a template" by incubating a template molecule with single-stranded DNA-binding protein (SSB) prior to an enzymatic sequencing reaction. The disclosure of

Studier et al. is directed to improving primer binding, and thus the SSB is added with the primer in the primer annealing step, as disclosed at Col. 1, l. 44-62, Col. 2, l. 36-40 and Col. 3, l. 26-32 of Studier et al.

Specifically, the template molecule, SSB and primers are incubated before addition of polymerase, consistent with the teaching of Studier et al. to use SSB to promote alignment of primers on the template. In the presently claimed invention, SSB is included in a polymerase reaction to improve the efficiency of the method of identifying a base at a target position. Thus in contrast to the prior art methods, in the present invention SSB is added after hybridization of the primer to the template, as disclosed in the specification, for example at page 15, lines 1-4 and Claim 9.

Moreover, Studier et al. specifically teach away from changing the order of addition of the SSB, because undesirable secondary priming was detected when the SSB was added to a pre-equilibrated mixture of DNA and hexamers. Studier et al. at Col. 9, lines 24-32.

In the interest of advancing prosecution, Claim 1 has been amended to recite that nucleotide incorporation is detected by monitoring the release of inorganic pyrophosphate. Claim 6 has been canceled without prejudice, and Claim 7 has been amended to correct its dependency.

The subject matter of amended claim 1 is not rendered obvious by the cited references. Studier et al. teach that SSB is useful only in certain types of sequencing reactions, such as primer walking with contiguously annealing hexamer sets (Col. 5, l. 24 – Col. 6, l. 21), sequencing by hybridization using arrays of oligonucleotides (Col. 6, l. 24-39) and template-directed ligation (Col. 6, l. 42-57). All of these methods require a plurality of primers. In these methods, sequencing information is determined, for example from sequence ladders.

One would not have been motivated to substitute the pyrophosphate detection of Nyren et al. in the method of Studier et al., because Studier et al. teach that SSB is useful only in methods that require a plurality of primers. Specifically, Studier et al. teach at Col. 10, l. 42-43 that, in the presence of SSB, priming by individual hexamers was "was almost always strongly suppressed." The methods of Studier et al. require a plurality of hexamer primers, and thus would be difficult to modify for detection of pyrophosphate. Pyrophosphate detection as taught by Nyren et al. requires

that the signal be generated and detected as each individual nucleotide is incorporated. Nyren et al. at page 3, lines 2-12. It would be difficult, if not impossible, to detect each nucleotide as it is incorporated in the methods of Studier et al., because multiple priming and extension is occurring, and thus multiple nucleotides are simultaneously being incorporated.

Claims 1-7 and 10 are thus not rendered obvious by Studier et al. or the combination of Studier et al. and Nyren et al. Claim 8, which depends from amended Claim 1, is not rendered obvious by Studier et al. in view of Schultz et al., since the references fail to teach or suggest detection of pyrophosphate.

In view of the foregoing comments and amendments, withdrawal of the rejections of Claims 1-8 and 10 under 35 U.S.C. § 103(a) is respectfully requested.

Claim 15 has been rejected under 35 U.S.C. § 103(a) as allegedly rendered obvious by Studier et al. in view of the Stratagene Catalog (1988) p. 39. The Examiner has alleged that it would have been obvious to combine the reagents used in the method of Studier et al. into a kit format. In the interest of advancing prosecution, Claim 15 has been amended to replace "means of incorporation" by "luciferase." The use of luciferase is not taught or suggested by Studier et al. Withdrawal of the rejection of Claim 15 is respectfully requested.

In view of the foregoing remarks and amendments, it is respectfully submitted that the present application is in condition for allowance. Entry of the present amendment and favorable consideration of all pending claims are earnestly solicited.

Respectfully submitted,

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